PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P032045WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/04848	International filing date *(day/month/year)* 02.10.2003	Priority date *(day/month/year)* 11.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/095		
Applicant CHIRON SRL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.05.2004	10.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Wagner, R Telephone No. +49 89 2399-7357

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/04848

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-44 as originally filed

Claims, Numbers

1-31 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 28

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 28

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,4,5-15,18,21-25,30,31
	No:	Claims	1,3,16,17,19,20,26,27,29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27,29-31
Industrial applicability (IA)	Yes:	Claims	1-27,29-31
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the opinion

The sequence listing filed on 11.02.2004 according to the required specifications was filed after the filing date and is therefore not considered as being part of the description (Rule 13^{tr}.1 (f) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 28 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.

1. Reference is made to the following document/s/:

   D1: WO 01/64920
   D2: WO 01/64922
   D3: Comanducci et al., J. Exp. Med, vol. 195, no. 11, pp.1445-1454.

2. For the assessment of the present claim 28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable methods comprising surgical steps.

3. Independent claim 1 is directed to a composition, which is able to induce a bactericidal antibody response against two or more of hypervirulent lineages A4, ET-5 and lineage 3 of Neisseria menigitidis serogroup B. The claim does not include a definition of bactericidal response and must therefore be construed to

include compositions which generate antibodies able to kill bacterial strains of at least two of the defined lineages.

D1 discloses a composition comprising the hybrid ΔG287-953 (Seq. Id. No. 7 in the present application). Said composition is able to generate bactericidal antibodies against MC58 (lineage ET5) and 394/98 (lineage 3), see table on page 24. In addition said composition inherently has the ability to kill 75% of the tested strains of lineages ET-3 and 3 (see table on page 34 of the present application). The polypeptides of D1 are obtained by recombinant expression (see also item 1 of further Remarks). The polypeptides of D1 are intended for the use as vaccines. Therefore D1 anticipates the subject-matter of claims 1, 3, 16, 17, 19, 20, 26, 27, 28, , 29 (Article 33(2) PCT).

D2 is a parallel application to D1 and discloses the same relevant subject-matter as D1. D2 discloses the hybrid ΔG287-953 (Seq. Id. No. 7 in the present application) on page 37 and the data relating to the bactericidal activity of antibodies induced by the polypeptides on page. Therefore D2 anticipates also the subject-matter of claims 1, 3, 16, 17, 19, 20, 26, 27, 28, 29 (Article 33(2) PCT).

The subject-matter of claim 2 is new (Article 33(2) PCT) because the prior art does not disclose a composition comprising from 2 to 10 polypeptides. The difference between the subject-matter of claim 2 and D1 or D2 is the fact that in claim 2 at least 2 polypeptides are present in a composition. D1 and D2 disclose several polypeptides which are able to generate a bactericidal antibody response against hypervirulent Neisseria meningitidis serogroup B but they are not combined in one composition. The technical problem to be solved is the provision of a vaccine which provides a broader immunity than a single polypeptide. The skilled person would have combined several of the polypeptides or fusion polypeptides of D1 or D2 to solve said problem. Therefore the subject-matter of claim 2 does not involve an inventive step (Article 33(3) PCT).

The same reasoning applies to independent claim 4, which is directed to a composition comprising five meningococcal antigens, which are all disclosed in D1 and D2. The present application does not provide any data showing a surprising effect (which would extend beyond the expected increase of the broadness of the vaccinal protection) due to the combination of said five antigens. It appears that the additional features of dependent claims 5-15 do not confer an inventive step

on the composition (Article 33(3) PCT).

4. The subject matter of dependent claims 18, 21 is new (Article 33(2) PCT). D1 and D2 disclose the protein 741, but not protein 936. D1 and D2 disclose fusion proteins comprising protein 741 and several other N. meningitidis proteins as fusion partners. The skilled person does not have any indication that said fusion protein is able to generate elevated bactericidal antibody titres (see table on page 33). Therefore an inventive step can be acknowledged for the subject-matter of claims 18 and 21.

5. Dependent claims 21-25 are new (Article 33(2) PCT). As the present application does not show any surprising technical effect which could be attributed to the addition of saccharide antigens or antigens from Streptococcus pneumoniae to a composition comprising the polypeptides disclosed in D1 and D2, an inventive step cannot be acknowledged for the subject-matter of claims 21-25 (Article 33(3) PCT).

6. Claim 30 is directed to a process for purifying soluble NadA and is not disclosed in the prior art (Article 33(2) PCT) . D3 discloses NadA and a different process of purification involving C-terminal Histidine fusion. In order to purify soluble NadA without C-terminal Histidine the skilled person would envisage the purification process disclosed of claim 30 which consists of standard steps and does not produce any surprising technical effect. Therefore the subject-matter of claim 30 does not involve an inventive step (Article 33(3) PCT).

7. The process of claim 31 for producing the new and inventive hybrid protein of claim 21 is also new (Article 33(2) PCT) and inventive (Article 33(3) PCT).

8. As the validity of the priority documents could not be verified at the moment of the present preliminary examination, the published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 03/020756	13.03.2003	06.09.2002	06.09.2001
WO 03/010194	06.02.2003	26.07.2002	14.05.2002

are considered as not being part of the prior art (Rule 64.1 PCT). However these

documents may be of importance regarding novelty in a subsequent national/regional phase.

FURTHER REMARKS:

1. The feature of claim 3 is not limiting the composition because the skilled person is not able to differentiate if a polypeptide which is in his hands was obtained by a recombinant method or by another procedure. Therefore claim 3 is not clear (Article 6 PCT).